REMARKS

Claims 1, 3, 4, and 21 are pending in the application. Claims 2 and 5-20 have been cancelled without prejudice or disclaimer. Claims 1 and 21 are amended. Accordingly, upon entry of the present amendment claims 1, 3, 4, and 21 are pending.

Support for the amendments is found throughout the claims and specification as originally filed, and is discussed in more detail below. Specifically, support for the amendments is found in the originally filed specification at page 9, lines 25-29 and at page 4, lines 1-13. No new matter has been added.

Amendment of the claims herein is not to be construed as acquiescence to any of the rejections/objections set forth in the instant Office Action, and was done solely to expedite prosecution of the application. Applicants hereby reserve the right to pursue the claims as originally filed, or similar claims, in this or one or more subsequent patent applications.

Claim Rejections – 35 U.S.C. § 112

Claims 1, 3, 4, and 21, which are directed to genetic screening methods that are useful or predictive for a predisposition to Alzheimer's disease or diagnostic of Alzheimer's disease, are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully disagree and traverse the rejection.

Claims 1 and 21 now recite that the human subject is suspected of being at risk for or of having Alzheimer's Disease (AD) and that the presence of the allele substitution(s) is statistically significant. Thus, the claims are directed to genetic screening methods where the presence of the recited allele substitution(s) are statistically significant for predicting a predisposition to Alzheimer's disease or diagnose Alzheimer's disease in a human subject.

The Examiner has stated that "the specification does not provide guidance on how to determine if this person has AD or is just at risk of developing AD." (Office Action at page 6, last sentence). Applicants respectfully disagree. Applicants specification clearly enables the skilled person, i.e., a skilled medical practitioner with an understanding of AD, to distinguish those having a predisposition to Alzheimer's disease from those subjects that have Alzheimer's disease. The MPEP states that

> Detailed procedures for making and using the invention may not be necessary if the description of the invention itself is **sufficient to permit those skilled in the art to make and use the invention**. [MPEP §2164; emphasis added]

and,

> The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." *In re Wright,* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). **Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art.** Further the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). [MPEP §2164.08; emphasis added]

Moreover, the claims have been amended to recite that the subject is suspected of having (e.g., is presenting symptoms consistent with AD) or is at risk of having AD (e.g., a young person who does not present symptoms consistent with AD).

In the present case, it would be apparent to the skilled person (e.g., a medical practitioner who understands the mechanism of diagnosis and who understands AD) how to make and use the claimed invention. .The person skilled in the art would be able to recognize, for example, that AD is a disease of ageing and so a result in a healthy 20 year old is suggestive of a predisposition to AD, while the same result in an 80 year old would be diagnostic of the presence of AD. As this is part of the common general knowledge of the skilled person, this does not need to be explicitly spelled out in either the claim or the specification. Nevertheless, Applicants' specification still clearly satisfies the enablement requirement. As supported by case law,

> **Claims are not rejected as broader than the enabling disclosure under 35 U.S.C. 112 for noninclusion of limitations dealing with factors which must be presumed to be within the level of ordinary skill in the art**; the claims need not recite such factors where one of ordinary skill in the art to whom the specification and claims are directed would consider

> them obvious. *In re Skrivan*, 427 F.2d 801, 806, 166 USPQ 85, 88 (CCPA 1970). [MPEP §2164.08; emphasis added]

Accordingly, Applicants respectfully request reconsideration and withdrawal of this basis for rejection.

The Examiner alleges that it is unpredictable whether a particular polymorphism of the invention is associated with Alzheimer's disease. In support of this assertion, the Examiner cites Bagnoli et al. (Neuroscience Letters 418:262-265, 2007; "Bagnoli") and Capruso et al. (Experimental Gerontology 39:1567-1573, 2004; "Capruso"), and alleges that the references conflict with the data presented in Applicant's specification (Office action mailed November 4, 2008, page 9, fourth full paragraph). Bagnoli and Carpruso are both **post-filing date** references.

The M.P.E.P. provides helpful guidance concerning the use of post-filing date references. In particular, the MPEP §2164.05(a) states

> In general, **the examiner should not use post-filing date references to demonstrate that the patent is non-enabling**. Exceptions to this rule could occur if a later-dated reference provides evidence of what one skilled in the art would have known on or before the effective filing date of the patent application. *In re Hogan*, 559 F.2d 595, 605, 194 USPQ 527, 537 (CCPA 1977). [emphasis added]

Contrary to this guidance, the Examiner cites post-filing date literature to support the assertion that the art is unpredictable and that in view of this unpredictability undue experimentation would be required to practice the invention. Applicants respectfully disagree with this basis for the rejection.

Although Bagnoli and Capruso present findings that purportedly differ from the findings described by Applicants, Bagnoli and Capruso provide no teaching that would in any way invalidate Applicants' findings or those of other studies demonstrating similar results. Thus, Bagnoli and Capruso fail to provide "reason to doubt the objective truth of the statements contained" within Applicant's specification as required to support the enablement rejection. M.P.E.P. 2164.04.

In fact, Bagnoli and Capruso acknowledge that their results may not be definitive and that there are a number of factors that could cause their results to differ from those present in the prior art. For example, Bagnoli states:

> Three studies carried out on Italian and Chinese populations have shown that IL10 polymorphisms are a genetic risk factor in the development of AD, demonstrating that IL10 -1082A, 0819T and -592A alleles are significantly over represented in AD patients compared to non-demented controls. However, other studies have not been able to replicate these results and it has been suggested that **the role of the IL10 gene in AD susceptibility <u>may</u> be limited to certain populations, indicating the need of <u>further studies</u>** [page 262, right column, lines 14-22; emphasis added].

Similarly, Capruso acknowledges that "regional European differences in genotype and allele frequencies of the Il-6-174 g/c promoter polymorphism may explain in part controversial findings on this polymorphism in AD in various European studies (Abstract)." Capruso does not regard the published findings as definitive, but suggests that "further studies on larger and different populations, controlling for ethnic and geographic variability" should be conducted to explore regional variations in IL-6 genotype and allele frequencies (page 1572, right column, last paragraph).

Although Applicant's have shown a statistically significant correlation between -1082A IL-10 and Alzheimer's disease, the Examiner nevertheless asserts that the association of -1082A of IL-10, 174C of IL-6, ApoE4 carrier or 1082A IL-1 with Alzheimer's disease is unpredictable because "the specification does not teach a large sample size, analyze different ethnic groups or provide confidence levels greater than 95% for 1082A of IL-10, 174C of IL-6, ApoE4 carrier or -1082A IL-1 . . ." Although large sample size studies are of interest in the epidemiology of any human disease, in clinical genetics there is an increasing drive to identify particular genetic variations that correlate with disease in particular subpopulations. The finding that a particular marker has been positively associated with disease in a small sample of carefully and closely matched individuals is not negated by contrary observations in a large population of unmatched individuals. Even so, Applicants respectfully submit that further experimentation to confirm Applicants' results in a larger population would be considered routine in the field of diagnostics and does not constitute undue experimentation (MPEP §2164.01).

Applicants have discovered that certain patients that have -1082A IL-10 are at an increased risk for developing Alzheimer's disease, and that use of -1082A IL-10 together with other Alzheimer's disease markers (e.g., 174C of IL-6, ApoE4 carrier or -1082A IL-1) is likely to be usefully in assessing a subject's Alzheimer's disease risk. In view of these results, ***Applicants have fully enabled the claimed subject matter for a subject suspected of being at risk for or having Alzheimer's disease***, as presently recited in the claims.

In contrast to Bagnoli and Capruso, post-filing date literature (References submitted with Response filed July 15, 2008) confirm the studies upon which the Applicants' claimed invention is based. In particular, the scientific publications cited by Applicants indicated that the gene polymorphisms presently claimed are indicative of the presence or absence of a predisposition to develop Alzheimer's disease. See, for example, Combarros et al *J. Neural Transm.* **2008** Jun:115 (6) pp 863-7 (Epub 2008 Feb 26) "Aromatase and interleukin-10 genetic variants interactively modulate Alzheimer's disease risk." ("Combarros")) or Ma et al *Neurobiol Aging* **2005** Jul: 26(7) pp 1005-10 (epub 2004, Nov 23) "The Association Between Promoter Polymorphism of the Interleukin-10 gene and Alzheimer's disease." or Infante et al. *Neurology.* **2004**; 63: pp1135-1136 "Gene–gene interaction between interleukin-6 and interleukin-10 reduces AD risk." ("Ma") (Copies submitted with Response filed July 15, 2008).

Because Alzheimer's disease can only be definitively confirmed post-mortem there are considerable differences in the clinical and psychometric methods used to establish a diagnosis of Alzheimer's disease and to assess disease progression, while a subject or patient is still alive. Accordingly, it is not surprising that certain differences may exist between groups assaying the predictive value of various genetic markers in predicting Alzheimer's disease risk. Such differences may be attributable to variability in the clinical and psychometric methods used to assess and select patients and controls.

The Examiner maintains that it "is the totality of the evidence in the prior art … that gives reasons for the uncertainty of the enablement...." (Office Action at page 15). The Examiner cites *In re Wright* 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993) for the proposition that post-filing art can be used to show that "a particular invention is not possible years after the filing date . . . would be evidence that the disclosed invention was not possible at the time of filing." However, as detailed above, Bagnoli and Capruso fail to indicate

that Applicants' invention is impossible. They merely present data that purportedly differs from the findings described by Applicants.

In *Wright*, the court found that results from one virus in one animal could not be extrapolated to all viruses with all living organisms because the post-filing art showed that the viruses activity was too unpredictable to permit extrapolation. The facts of Wright are readily distinguishable from the present case because Applicants claims do not require extrapolation. Applicants provide working examples showing that the claimed polymorphisms are statistically correlated with Alzheimer's disease. Given the presence of these working examples, Applicants have clearly enabled the full scope of their claims.

Applicants invite the Examiner's attention to MPEP §2164.05 which states that

> The examiner must then weigh all the evidence before him or her, including the specification and any new evidence supplied by applicant with the evidence and/or sound scientific reasoning previously presented in the rejection and decide whether the claimed invention is enabled. The examiner should **never** make the determination based on personal opinion. The determination should always be based on the weight of all the evidence. [emphasis in MPEP]

In the present case, the Examiner appears to give undue weight to the purportedly contradictory results described by Bagnoli and Capruso, while dismissing the results described by Combarros, Infante and Ma, which support the enablement of the claimed methods. This is improper. The M.P.E.P. cautions that Applicants' disclosure **must** be taken as being in compliance with the enablement requirement of 35 U.S.C. 112 in the absence of evidence to the contrary. M.P.E.P. 2164.04.

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must be taken as being in compliance with the enablement requirement of** 35 U.S.C. 112, **first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein** which must be relied on for enabling support.

Given that Applicants' have provided strong countervailing evidence in support of their disclosure, the Office has failed to establish a reasonable basis to question enablement. Accordingly, this basis for the enablement rejection should also be withdrawn.

In sum, Applicants' disclosure clearly satisfied the enablement requirement. Applicants describe methods for screening subjects for Alzheimer's disease by extracting genomic DNA from blood samples and analysing the sequence of the IL-10 and IL-6 promoters using sequence-specific primers (pages 22-23). Statistical analysis of genotype and allele frequencies showed that there was a higher percentage of IL-10 -1082A and IL-6 -174C alleles among Alzheimer's patients (page 28, fourth full paragraph, and page 29, second full paragraph). Provided with this disclosure, one of ordinary skill in the art would be able to make and use the invention commensurate in scope with the claims because all of the methods needed to practice the invention, including methods for genetic analysis of DNA present in a patient sample, were merely routine and were well known at the time the application was filed as evidenced by the references cited by the Examiner, which describe the analysis of IL-10 and IL-6 polymorphisms and their association with Alzheimer's disease. Thus, the enablement rejection should be withdrawn.

CONCLUSION

Applicants respectfully request reconsideration and withdrawal of all rejections and allowance of the application with claims 1, 4-8, 10, and 11 presented herein.

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